

AD_____

Award Number: DAMD17-02-1-0245

TITLE: A Phase II Immunotherapeutic Trial: Combination Androgen Ablative Therapy Treatment for Advanced Prostate Cancer

PRINCIPAL INVESTIGATOR: Eugene D. Kwon, M.D.

CONTRACTING ORGANIZATION: Mayo Clinic Rochester
Rochester, MN 55905

REPORT DATE: June 2009

TYPE OF REPORT: Final Addendum

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE (DD-MM-YYYY) 01-06-2009		2. REPORT TYPE Final Addendum		3. DATES COVERED (From - To) 1 DEC 2008 - 31 May 2009	
4. TITLE AND SUBTITLE A Phase II Immunotherapeutic Trial: Combination Androgen Ablative Therapy and CTLA-4 Blockade as a Treatment for Advanced Prostate Cancer				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER DAMD17-02-1-0245	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Eugene D. Kwon, M.D. E-Mail: kwon.eugene@mayo.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Mayo Clinic Rochester Rochester, MN 55905				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited.					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT: The objectives of this study are to test whether CTLA 4 blockade + AA therapy can enhance clinical treatment responses in advanced prostate cancer patients relative to AA therapy alone. Study patients are randomized to 3 months of combined AA therapy + MDX-010 or versus AA therapy alone. To date, 46 patients have been enrolled and 42 randomized per protocol. An additional 84 patients have been screened and deemed ineligible for study. 29 patients now have sufficient follow-up to assess if any treatment effects may be occurring. In general, patients receiving combined AA + MDX-010 have exhibited greater PSA responses than patients receiving AA therapy alone. We have also observed that MDX-010 does not likely affect initial testosterone production but may delay testosterone recovery. Our preliminary studies also indicate atypical and favorable responses to combined MDX-010 + AA therapy including reversal of rising PSA, rapid resolution of obstructive urinary pathology and dramatic tumor downstaging resulting in unexpected 1 year disease-free patient status. Based on these preliminary observations, we believe that combined AA + MDX-010 treatment may encompass a promising approach to improve advanced prostate cancer treatment.					
15. SUBJECT TERMS Prostate Cancer					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	8	19b. TELEPHONE NUMBER (include area code)

Table of Contents

Cover	1
SF 298	2
Table of Contents	3
I. Introduction	4
II. Description of Overall Progress to Date.....	4
III. Problem Areas	7
IV. Description of Work to be Performed during Next Reporting Period	7
V. Administrative Comments.....	7
VI. Adverse Events	8

I. Introduction

This is an open-label randomized phase II trial in which 108 patients with advanced prostate cancer will be prospectively enrolled onto study. Upon enrollment patients will be immediately randomized to receive either: i) 3 months of concurrent AA therapy + MDX-010 (treatment group) or ii) 3 months of initial AA therapy alone (control group). Equal numbers of control and treatment group patients will be enrolled onto study.

II. Description of Overall Progress to Date

On February 13, 2004, the Mayo Clinic received notification from the USAMRAA that Modification No. P00001 for Grant No. DAMD 17-02-1-0245 was fully executed.

On March 25, 2004, a site visit was conducted by Medarex at which time it was noted that the drug administration language in the protocol also needed to be revised; administration of the study drug was no longer feasible in the manner written in the protocol.

A protocol modification dated April 8, 2004 was approved by the Mayo IRB on May 20, 2004. The revised protocol was subsequently submitted to the USAMRMC office. At this time, even though the protocol was considered active and open to enrollment, we were unable to proceed with study enrollment until we could obtain approval of the April 8, 2004, amendment, due to the changes in the drug administration language that were required.

Additional documents were subsequently requested by the HSRRB, and a Memorandum for Record (dated August 18, 2004) was generated in response to the amendments which the USAMRMC office received on June 14, 2004, and the additional information which Dr. Beitins of the HSRRB received on July 12, 2004.

A site visit from the USAMRMC office took place at Mayo Clinic Rochester on November 19, 2004.

On December 20, 2004, the USAMRMC office sent the draft recommendations from the December 8, 2004 HSRRB meeting to Dr. Kwon.

On January 4, 2005, the official HSRRB review of the protocol (dated December 8, 2004) was sent to Mayo. On January 26, 2005, Mayo responded to the HSRRB meeting requests; a revised protocol and consent dated January 25, 2005 were submitted to the HSRRB. On January 27, 2005, Dr. Kwon received notification from Dr. Beitins of the HSRRB that the documents submitted on January 26, 2005, were approved by the Acting Chair of the HSRRB. The revised protocol and consent form dated January 25, 2005, were subsequently approved by the Mayo IRB on February 24, 2005. An approval memorandum was issued to the Mayo contract specialist by Colonel Laura Brosch on March 15, 2005.

Recruitment activities commenced at Mayo in early April, 2005, and have been ongoing since that time.

In the course of our recruitment activities, we felt that the eligibility criteria were too narrow and limited our enrollment. We discovered that approximately 50 percent of the referrals that we received were patients who had recently been started on hormone therapy. Significant numbers were also excluded due to the “limited metastases” inclusion criteria. Therefore, we broadened the eligibility criteria to facilitate accrual without compromising the interpretation of outcome data pertaining to the treatment of patients with local or advanced prostate cancer receiving treatment on the study. In addition, we anticipated that the UCSF site would enroll 54 participants, however they were unable to screen or enroll any participants on this trial and were therefore removed as a study site.

A protocol revision dated August 28, 2006, was submitted to the Department of Defense on August 31, 2006. Protocol revisions consisted primarily of expanding the inclusion/exclusion criteria to include patients with any T stage prostate cancer, with or without metastatic disease (with the exclusion of central nervous system metastases), staged within 180 days of enrollment, including post-prostatectomy patients with a rising PSA and including patients who have initiated hormone therapy ≤ 21 days prior to enrollment. Protocol revisions also included removing the University of California, San Francisco as a study site since they had been unable to screen or enroll any participants.

These protocol and consent form revisions were approved by the Department of Defense Human Subjects Research Review Board on December 20, 2006, and by the Mayo Cancer Center RAS Committee on December 20, 2006; these revisions were approved by the Mayo IRB on January 11, 2007. This revision greatly facilitated enrollment onto our trial.

A protocol revision dated June 18, 2007, was submitted to the Department of Defense on July 24, 2007. Protocol revisions consisted primarily of further expanding the inclusion/exclusion criteria to include patients who have initiated hormone therapy ≤ 90 days prior to enrollment since we see a significant number of participants who have received hormone therapy within this time frame.

These protocol and consent form revisions were reviewed by the Department of Defense Human Subjects Research Review Board on October 17, 2007. The Board recommended that further revisions to the protocol and consent be made and that additional documents and information be provided. The requested protocol and consent form revisions were made and were submitted to the Mayo IRB. During the course of our IRB review process and after further consideration, our revision to the exclusion criterion expanding the acceptable length of hormone therapy to ≤ 90 days was subsequently retracted due to the fact that we have recently seen a very rapid increase in our accrual with the current ≤ 21 day period. On December 7, 2007, we received IRB approval of the 6-18-07 protocol amendment, which basically consisted of:

- clarification only to sections 6.1 (clarified that for those participants who are post radical prostatectomy, a rising PSA is acceptable) and 6.2 (clarified that current usage of systemic anticoagulation therapy is only an exclusion criteria for participants who elect to undergo the baseline transrectal needle biopsy of the prostate)
- editorial changes

- updated language in sections 11, 16, 17, 18, and 19 to reflect the current USAMRMC ORP HRPO language
- updates to sections 2.6.1, 2.6.2, 2.6.3, 2.6.5, and 8.10 to include the updated toxicity information on MDX-010, as per the revised Investigator Brochure (Version 10).

All requested documents and information and the further revised protocol and consent form were forwarded to the HSRRB on December 11, 2007.

Our technical progress report to the USAMRMC was submitted on December 21, 2007.

A scientific peer review of our clinical trial was conducted on January 28, 2008, and we received a Summary Statement of this review dated March 6, 2008. On April 11, 2008, we provided our detailed response to the Peer Review Panel Summary Statement. The Prostate Cancer Research Program (PCRP) provided additional guidance to us, and, as a result, revisions were made to the protocol on June 10, 2008. The PCRP-recommended revision consisted of amending the inclusion criteria to include only patients with >cT2c (N0M0). In addition, we reduced the number of timepoints when the PBMC samples are collected, and we defined disease progression for participants who previously underwent a radical prostatectomy prior to study enrollment.

The June 10, 2008 protocol amendment and Addendum 1 to Edition 10 of the Investigator Brochure were approved by the Mayo IRB on August 15, 2008, and subsequently by the HSRRB on September 24, 2008.

A revised Investigator Brochure (Edition 11) dated August 14, 2008, was received from Bristol-Myers Squibb on August 21, 2008, and was forwarded on to the HSRRB on August 28, 2008. This was approved by the Mayo IRB on October 16, 2008.

A protocol amendment dated January 26, 2009, and a revised Investigator Brochure (Amendment 1 to Version 11, dated January 16, 2009) were approved by the Mayo IRB on February 18, 2009, and were forwarded to the HSRRB on February 20, 2009. Protocol revisions consisted of changes to the exclusion criteria and revising the MDX formulation language.

The continuing review report was approved by the Mayo IRB on April 30, 2009, and was forwarded to the HSRRB on May 18, 2009.

We continued to aggressively work to accrue study participants, continued to maintain good working relationships with the staff urologists, residents, and PAs in the Department of Urology, and continued with the previously established recruitment activities. These activities consisted of:

- distributing printed flyers to staff urologists, residents, and physician assistants (PAs)
- posting study flyers on intra-clinic bulletin boards
- posting study flyers in all of the exam rooms
- sending weekly e-mail notifications to staff physicians, residents, and PAs
- scheduling individual one-on-one meetings with Dr. Kwon and the staff urologists
- presentations of the protocol at staff and resident meetings
- daily review of physician calendars for potential participants

- daily telephone calls to physicians, residents, and PAs each morning asking for referrals of any potential participants that they may see during the day
- networking with nurses, technicians, paramedical personnel, appointment schedulers, and other RN study coordinators within the Department of Urology

These efforts resulted in successful completion of study enrollment. Since the time of our last report, we have enrolled 18 additional participants on this protocol at Mayo Clinic Rochester and have considered an additional 9 potential participants who were deemed ineligible.

This brings our study enrollment to 117 with a total of 151 potential participants considered but deemed ineligible. We have randomized 108 study participants. Of these, 53 were randomized to the control arm and 55 were randomized to the treatment arm; 29 control arm participants have crossed over to treatment.

Of the randomized 108 study participants, roughly 100 have sufficient initial follow-up to assess whether any treatment effects may be occurring: 50 patients are regarded as "control" patients and have only received hormone therapy (removal of testosterone only, which is considered standard of care); 50 patients are considered "test" subjects and have received hormone therapy in combination with MDX-010 (an immune-boosting experimental agent that has been shown to promote cancer regression).

Thus far, those 50 patients who have received the combination of hormone therapy along with MDX-010 have generally demonstrated greater responses than patients that have received only hormone therapy alone. Specifically, the 50 test subjects have experienced faster declines in their PSA (prostate specific antigen) which is a blood marker that correlates with the extent of prostate cancer within their body. This suggests that MDX-010 causes hormone therapy to work more effectively than using hormone therapy alone.

Additionally, we have observed that some of the test subjects experienced a more prolonged response (diminished PSA) relative to those that received hormone therapy alone. Based on these preliminary observations, our strong hunch is that patients who received hormone therapy plus MDX-010 treatment (immune boosting) may be deriving a benefit from the experimental form of therapy beyond that which occurs using standard treatment (which is hormone therapy alone).

III. Problem Areas

None.

IV. Description of Work to be Performed During the Next Reporting Period

We plan to continue with the study as per the protocol dated January 26, 2009.

V. Administrative Comments

None.

VI. Adverse Events

ADVERSE EVENTS	GRADE	FREQUENCY
Pruritus	1	13
Fatigue	1	30
Hot Flashes	1 & 2	All
Low Hemoglobin	1	10
Depression	1	2
Diarrhea	1	10
Diarrhea with hematochezia	2	4
Diarrhea with hematochezia	4	4
Ureteral Obstruction	3	1
Increased ALT and AST	1 & 2	16
Headache	1	1
MRSA		1
Insomnia	1	1
>BUN, uric acid	1	2
Colon adenocarcinoma		1
>Alk Phos, amylase, lipase	1	5
>Glucose	1 & 2	15
<Platelets	1	2
>LDH	1	8
Left sided jaw pain	1	1
Hematuria	1	1
Head Cold	1 & 2	2
Shedding Darkened Skin Moles		3
> Calcium	1	5